DR. HERBERT McKENNIS, JR.
DEPT. OF PATHOLOGY, UNIV. OF MIAMI
15655 SW 127TH AVENUE
MIAMI, FL 33177

Exhibit 1

February 11, 1982

Hadrian R. Katz, Esquire
Arnold & Porter
1200 New Hampshire Avenue, N. W.
Washington, D. C. 20036

Dear Mr. Katz:

You have asked for my comments on a series of papers prepared by various authors on behalf of Brown & Williamson Tobacco Corporation, namely "Submission to the Federal Trade Commission on Behalf of Brown & Williamson Tobacco Corporation," a letter of October 22, 1981 from Dr. Gio Batta Gori of the Franklin Institute Policy Analysis Center to Martin London, Esquire, and "Use of Cotinine Blood Concentration as a Detection Method of Nicotine Delivery with Cigarette Smoking," by Dr. T. D. Darby and Dr. James E. McNamee of the University of South Carolina School of Medicine. In particular, you have asked whether the experiment described by Brown & Williamson involving measurements of plasma cotinine levels */ permits one to draw

*/ There is a certain inherent confusion in the Brown & Williamson papers caused by the authors' apparently interchangeable use of the words "blood" and "plasma." See for example pages 1, 4, 5, and 6 of the Darby and

[Footnote continued on following page.]

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conclusions about the relative smoke (nicotine) deliveries of particular brands of cigarettes.

My principal conclusions are two-fold:

First, in my professional judgment, as one who has been doing work in this area for over 20 years, the current state of the scientific art simply will not support Brown & Williamson's conclusions that plasma (blood) cotinine levels can serve alone to measure lung intake of nicotine from cigarettes. The process of nicotine metabolism is far too complex and includes too many only partially understood variables to permit meaningful comparisons of nicotine absorbed from various cigarette brands. Brown & Williamson is able to draw conclusions only by making a number of simplifying assumptions -- that all nicotine

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[Footnote continued.] McNamee monograph. If we are to consider the Gori letter of October 22, 1981 as the prime source, we conclude that plasma would be intended throughout. Since samples of whole blood were available when obtained from the subjects of the Gori study, it is to be regretted that cotinine concentration of whole blood was not determined to make comparisons possible. It is well known that many substances tend to concentrate in the plasma and are carried or bound to plasma protein. Some authors (unpublished observations) consider that cotinine is bound to blood plasma protein and that this affects the long half-life of cotinine.

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comes from cigarettes, that of all nicotine in smoke that is absorbed into the lungs, 70% turns promptly into cotinine, and that all cotinine distributes itself evenly throughout the body and disappears with a half-life of 30 hours -- all of which appear to be unsound and unsupported on a general basis.

Second, while the paucity of experimental data and procedural details makes it difficult to comment at length upon the specific techniques employed by Gori, it appears that his methodology was poor. In particular, the failure to control a number of key variables such as the urinary pH of test subjects, and the rather simplistic manner in which gas-chromatographic analyses were conducted, leads me to be suspicious of the data generated in Gori's experiment.

In general, nicotine absorption in a smoker's lungs will vary from individual to individual, and probably in a nonlinear fashion for any given individual. */

*/ I should note that it is partially speculation at this point in the development of the science to indicate where nicotine that arises in the human body had its source.

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The pH of the smoke and particle size of the intake are probably significant determinants of nicotine absorption. After the nicotine is absorbed, the timing and extent of its conversion to cotinine will also vary from individual to individual, and probably nonlinearly for any given person. Genetic, nutritional, age, and blood chemical factors are all significant in determining the metabolic route of the nicotine. In particular, urinary pH is a primary determinant of direct nicotine excretion; low urinary pH will lead to greater nicotine excretion and concomitantly low cotinine formation.

[Footnote continued.] Certainly tobacco is one principal source. Other possible sources include tomatoes (Dawson, Solt, and Christman, Ann. N.Y. Acad. Sci., 90, 7, 1960) peppers, and eggplant. Currently, there are some 400 species of tomato plants commercially available in the United States, and data on the nicotine content of most of these species is very scanty. The same can be said about data on a number of other plant sources, and people are just beginning to report the presence of cotinine in various types of plant material not closely related to tomatoes. The possibility of nicotine or cotinine being absorbed from sources other than cigarette smoke makes it extremely difficult to draw conclusions about cigarettes from experiments such as those performed by Brown & Williamson.

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The anonymous author of the Brown & Williamson Submission to the FTC states that cotinine is the "first and primary" metabolic product of nicotine. That is a serious misconception. Soon after my group first identified (McKennis, Turnbull, and Bowman, J. Amer. Chem. Soc. 79, 6342, 1957) cotinine as a metabolite of nicotine, Hucker, Gilette and Brody (Nature, 183, 47, 1959; J. Pharm. Exp. Therap., 129, 94, 1960) suggested that 5'-hydroxynicotine was an intermediate that preceded cotinine. Hence, it has been known for many years that cotinine itself cannot be the first metabolic product. It has also been noted that 5'-hydroxynicotine may be in equilibrium with 4-3-pyridyl-4-methylaminobutyric aldehyde. These substances themselves, as well as the corresponding methylamino acid, therefore may be precursors of cotinine. Later, Murphy (J. Biol. Chem. 248, 2796, 1973) proposed that nicotine Δ-1'(5')-iminium ion was an intermediate in the series of compounds which leads to the formation of cotinine. Since that time, numerous other authors have discussed this subject. Nicotine metabolism is a very complex process, and the

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Brown & Williamson papers are unscientific in their assertions to the contrary.

After cotinine is formed in the body, its persistence is likely to vary from individual to individual, and nonlinearly for any given person. Cotinine may tend to bind to proteins, but the degree of binding is likely to depend on the presence of other chemicals in the blood. Accordingly, rather extensive analyses of relevant chemicals in the blood would be necessary before drawing any conclusions from cotinine levels.

Some comment should perhaps be made regarding Gori's effort to have each test subject serve as his own control. While there is a certain abstract logic to that proposition, in practice it would be necessary to control diet, urinary pH, urine flow rate, stress, and many other factors for the individual test subjects to assure that no systematic errors were being built into the study. In particular, it is difficult to understand Gori's apparently complete indifference to the urinary pH of his subjects. As early as 1942, Haag and Larson (J. Pharmacol. Exptl. Ther. 76, 235,

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1942) noted the significance of this variable, and the same or similar studies have been repeated in many countries of the world.

Truhaut and DeClercq (Comt. Rend. 253, 1956, 1961) have presented evidence for the mammalian formation of dihydrometanicotine as a nicotine metabolite. We are not at this point aware of any evidence that dihydrometanicotine occurs as a result of the metabolism of nicotine in human urine, but that would appear to be a reasonable hypothesis. Some tobaccos are said to be high in metanicotine.

In man, cotinine can be metabolized to cotinine methonium ion (McKennis, Turnbull, and Bowman, J. Biol. Chem., 238, 719, 1963), and in the dog nicotine is subject to methylation of the nitrogen on the pyridine ring with the resultant urinary excretion of nicotine isomethonium ion. Nicotine metabolism in man frequently tends to parallel that in the dog, and therefore some investigation should be made into the possible excretion of nicotine isomethonium ion in man. Until such questions are answered, the methodology employed by Gori simply cannot be considered sound.

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A number of the principal problems with the Brown & Williamson analysis can be illustrated by a detailed examination of Table 1 of the Darby and McNamee paper. The table is entitled "Factors Affecting the Determination," although it is not clear whether "determination" refers to the mathematical results which are based upon a number of shaky biological assumptions, or the determination experimentally of some of the factors important to the subject.

Item 1 in Table 1 is "Sensitivity and accuracy of the method used for determination of cotinine blood values," and it raises a serious question about the experimental laboratory work performed by Gori. There is simply no way of knowing in Gori's study whether the cotinine peaks in the gas-chromatographic determinations represent pure cotinine, or cotinine plus other compounds which may be present in the blood. Among the other compounds that may be, and frequently have been, mistaken for cotinine are other metabolites of nicotine. For instance, in a paper by Pilotti, Enzel, McKennis, Bowman, Dufva, and Holmstedt (Beitr. Tabakforsh. 8,339, 1976),

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it was noted in three different gas-chromatographic columns that allohydroxycotinine, one of the many pyridine metabolites of nicotine, appears with the same retention time as cotinine. In each instance where one is setting up gas-chromatographic determinations of cotinine, irrespective of the nominal composition of the column, it appears necessary to run numerous controls and determine whether or not the cotinine peak from biological material actually represents pure cotinine. This can be handled by use of mass spectrometry, infrared spectroscopy, paper chromatography, thin-layer chromatography, or the like. Gori's failure to include such controls precludes reliance upon his data.

Item 2 of Darby and McNamee's Table 1, "Cotinine biological half-time," and Item 9, "Conversion half-time for nicotine metabolism to cotinine," can perhaps be discussed together. Brown & Williamson assumes that precisely 70% of nicotine is converted to cotinine, essentially immediately, and that cotinine then has a half-life in the body of 30 hours. These assumptions appear to be completely arbitrary, and are inconsistent with a number of complications in nicotine metabolism.

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For example, Feyerabend (Workshop on Nicotine, Svenska Tobac. A.B., Stockholm, 1974) reported that following pulse injection of nicotine intravenously over a period of 10 minutes, nicotine concentrations in saliva rose to a level of approximately 300 nanograms per milliliter, while the blood concentrations of nicotine never exceeded 25 nanograms per milliliter. As pointed out in a paper by Castro, Monji, Ali, Yi, Bowman, and McKennis (Eur. J. Biochem. 104, 331, 1980), this excretion of nicotine into the saliva leads to the possibility of reintroduction of nicotine by way of the gastrointestinal tract. Other sources for the reabsorption of nicotine including the buccal cavity itself need to be considered. */

*/ In light of the saliva data and related studies, it is surprising that Darby and McNamee state (page 4, lines 13 and 14) that cotinine, being a small lipid molecule, distributes within all tissues in a volume equal to the total body water content. Such a sweeping and surprising generalization would require considerable experimental support. If one is to call cotinine a small lipid molecule -- and the dictionary will permit this -- one could equally well call benzene and related compounds small lipid molecules, and the latter certainly do not distribute themselves as Darby and McNamee suggest. Although there are limited amounts of data on the distribution of cotinine in various tissues which probably could be improved with modern analytical methods, the problem seems to lack solution at this point.

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That nicotine can be converted to nicotine 1'-N-oxide is another factor that must be considered in drawing conclusions about nicotine metabolism to cotinine. Once nicotine 1'-N-oxide has been formed in man, it can undergo a number of different metabolic routes including reconversion to nicotine and possibly conversion to cotinine N-oxide which has been described as a mammalian metabolite of nicotine by Dagne and Castagnoli (J. Med. Chem., 15, 840, 1970). It can be noted in passing that if cotinine N-oxide is injected into a gas-chromatographic apparatus under conditions resembling those described in the Gori study, there will likely be conversion of cotinine N-oxide to cotinine and this will lead to an abnormally high level of apparent cotinine in plasma. This factor appears to have escaped the attention of the Brown & Williamson authors.

Another source of possible influence of nicotine 1'-N-oxide may be found in the paper of Kline and Gorrod (Eur. J. Drug Metab. and Pharamacokinetics, 51, 1978). In Table 1 of that study, it was noted that 8 of the 47 male subjects excreted (on a weight basis) more nicotine

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1'-N-oxide than cotinine in the urine during the 24 hours after smoking tobacco-containing cigarettes. The same was true of at least 5 of the female subjects in that study, and in one case, excretion of nicotine 1'-N-oxide was more than twice that of cotinine.

Items 3, 4, and 5 of Darby and McNamee's Table 1, "Number of cigarettes smoked per day," "Variation in daily cigarette smoking pattern," and "Inhalation pattern of the individual smokers used in the study," include footnotes stating that the items can be minimized or corrected on the basis of alveolar carbon monoxide data. That may well be true in theory, but it is essentially impossible in practice. People have been struggling for at least 20 years to justify the use of carboxyhemoglobin or alveolar carbon monoxide levels to determine those very things. Despite many attempts at justification and many attempts at verification, this procedure still appears to be shaky. It remains a fact that being caught in a traffic jam can affect carbon monoxide levels as much, or more, than cigarette smoking.

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Item 7 of Darby and McNamee's Table 1 notes body weight and surface area variations among the subjects in the experiment. If those facts are known to affect the results, as appears likely, Brown & Williamson's papers would appear to require some discussion and interpretation in those areas.

Item 8 of Darby and McNamee's Table 1 concerned the sex of the subjects. The two groups in the experiment directed by Gori included both female and male subjects, and Gori noted that the subjects were healthy. Since pregnancy is not a disease state, one should note the experiments of Kline and Gorrod (Eur. J. Drug Metab. and Pharmacokinetics, 87, 1978) where it was noted that the urinary excretion ratio for cotinine to nicotine 1'-N-oxide in the 24-hour period was 6.56. This figure was almost four times that obtained in a control group of nonpregnant females. While the pregnant subject group was rather small, the published data point to another important gap in the Gori data reports.

All in all, very little has been done in man to permit one to assign a general figure for the conversion

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of nicotine to cotinine following cigarette smoking. It is dangerous to conclude from serum cotinine values that a given amount of nicotine has been absorbed through the lungs of a given subject. It is even more dangerous to purport to be able to draw conclusions from such values about the relative performance of different brands of cigarettes under uniform smoking conditions. The day may come that experiments on human subjects such as those performed by Gori will provide useful information about specific cigarettes. The current level of science, however, does not yet permit this -- even in studies performed with substantially more care and precision than that evidenced by Brown & Williamson.

Sincerely yours,

Herbert McKennis, Jr.

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